DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5 March 2008 has been entered.

Status of Claims

2. The amendment filed on 5 March 2008 has been entered into the record and has been fully considered.

3. Claims 15 and 40 are amended. Claims 25, 26, 38 and 39 are withdrawn by Applicant. New claims 42-44 have been added.

4. Claims 1-5, 10-17, 23 and 29-35, and 40-44, drawn to a method for increasing muscle mass in an individual with a disease or disorder requiring an increase in muscle mass, by administering a pharmaceutical composition comprising an Activin Receptor Type IIB (ActRIIB) fusion polypeptide comprising an amino acid sequence of at least 95% identical to amino acids 23-138 of SEQ ID NO: 3 fused to an Fc portion of an antibody, wherein the fusion peptide is

capable of binding to the growth and differentiation factor-8 (GDF-8), are under consideration in the instant application.

Response to Amendment

Withdrawn objections and/or rejections

5. Upon consideration of the Applicant's amendment, all claim objections and rejections, not reiterated herein have been withdrawn, as overcome by cancellation and/or amendment of claims (5 March 2008).

6. Upon consideration of Applicant's persuasive argument, the rejection under 35 U.S.C. § 112, scope of enablement is withdrawn.

Declaration

7. The declaration submitted by Dr Paul Yaworsky under 37 CFR 1.132, filed 3 March 2008, providing data using the Duchenne's muscular dystrophy mouse model *mdx* is sufficient to overcome the rejection of claims 1-5, 10-17, 23 and 29-35, based upon 112, first paragraph (scope of enablement) in the previous office action (dated 19 November 2007 – Advisory action).

Information Disclosure Statement

8. The Information disclosure statement dated 8/23/07 is objected to because the Patent number US 6,472,179 in the patent database has an issue

date and Inventor different from that listed in the IDS, and hence, has been crossed off. Appropriate correction is requested.

New Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1-5, 10-11, 14-15, 17, 23, 29-30, 32-35, 40 and 42-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woolf et al. (International Application publication number WO 03/016475 A2, filed on 14 August 2002), in view of Lee et al (U.S. Patent No. 6,891,082, filed on 24 April 2001), in further

view of Feige et al (International Application publication No. WO 01/83525 A2, dated 8 November 2001).

11. Claims 1-5, 10-11, 14-15, 17, 23, 29-30, 32-35, 40 and 42-44, recite a method for increasing muscle mass in an individual (mammal or human) with a disease or disorder requiring an increase in muscle mass, by administering a pharmaceutical composition comprising an Activin Receptor Type IIB (ActRIIB) fusion polypeptide comprising an amino acid sequence of at least 95% identical to amino acids 23-138 of SEQ ID NO: 3 fused to an Fc portion of an antibody, wherein the fused peptide is capable of binding to the growth and differentiation factor-8 (GDF-8) (claims 1, 2, 14, 15, 23, 29, 30); wherein (i) the disease is a muscle disorder or a neuromuscular disorder such as muscular dystrophy or Duchenne muscular dystrophy (claims 3-5, 10-11); (ii) the Fc portion is unmodified or modified to reduce effector function, binding to an Fc receptor and complement activation (claims 32-35): the Fc fragment is a IgG1 or IgG4 (claim 40); and (iv) the amino acid sequence of the fusion peptide comprises at least 70 to 120 contiguous amino acids (claims 42-44).

12. Woolf et al. teach a polypeptide sequence of 512 amino acids that is 100% identical to amino acids 19-134 of SEQ ID NO: 1 (ActRIIB, see table on page 8 of the instant specification) of the instant specification (see SCORE sequence alignment – Appendix A). Woolf et al also teach pharmaceutical compositions comprising the polypeptide to be used as a pain medicament in an animal. Based upon the instant disclosure of the differences between SEQ ID

NO: 1 and SEQ ID NO: 3, it is noted that SEQ ID NO: 1 (amino acids 19-134) is at least 95% identical to SEQ ID NO: 3 (page 17, para 0051). Furthermore, a BLAST alignment of SEQ ID NO: 1 and SEQ ID NO: 3 show 98% homology in the amino acid sequence region 17-127 of SEQ ID NO: 1 and the sequence consisting of amino acids 21-131 of SEQ ID NO: 3 (Appendix B). Because the Woolf reference teaches 100% homologous sequence to SEQ ID NO: 1, the peptide of the art comprises of contiguous amino acid sequences of at least 120 amino acids. Therefore, the peptide taught by Woolf et al. falls within the scope of the claimed invention using SEQ ID NO: 3.

13. Woolf et al do not teach use of the peptide in binding and inhibiting GDF-8 activity, and increasing muscle mass in mammals having muscle disorder. Woolf et al. also do not teach fusion peptides with Fc portion.

14. Lee et al teach a method of increasing (modulating) muscle tissue in a subject, or a human requiring such treatment (abstract; col 1-2) by administering an agent that affects myostatin (GDF-8) signal transduction activity (abstract), wherein the agent is a peptide (col 3, line 3-4). Furthermore, Lee et al teach that ActRIIB specifically interacts with myostatin for proper regulation of muscle mass, and that dominant negative forms of ActRIIB comprising a soluble form of an extracellular domain or truncated forms can inhibit myostatin signal transduction (page 30, lines 59-65; col 72, lines 55, 56, 61-65). The reference further teaches the amelioration of severity associated with muscular dystrophy and

neuromuscular disorders, encompassed by modulating GDF signal transduction (col 4, lines 11-23).

15. Woolf et al and Lee et al. do not teach fusion peptides comprising of a Fc domain.

16. Feige et al teach fusion of biologically active peptides with the Fc domain of a IgG or IgG1 antibody (page 1, lines 13-14; page 2, Table 1). Feige et al further teach that the Fc domain can be native or modified (page 19, lines 3-18; page 20, lines 5-9), wherein the modification comprises a molecule or a sequence that lacks one or more Fc sites that affect pharmacokinetic properties of the drug, such as incompatibility with a selected host, binding to an Fc receptor, complement interaction etc. (page 19, 26-30; page 20, line 2).

17. It is to be noted that the limitations in the claims reciting the characteristics of GDF-8 activity (claim 1a) and the hybridization of the nucleic acid encoding the fusion polypeptide (claim 23) are inherent features. Furthermore, muscle disorders and muscular dystrophy inherently encompass Duchenne muscular dystrophy and diseases of damaged muscle (claims 5, 10-11).

18. It would have been obvious to the person of ordinary skill in the art at the time the claimed invention was made to modify the peptide of Woolf et al. or the extracellular soluble domain of ActRIIB peptide of Lee et al., by generating an Fc fusion protein as taught by Feige et al. The person of ordinary skill in the art would have been motivated to generate a fusion protein comprising ActRIIB and Fc portion of immunoglobulin, since such fusion proteins would be useful for the

preparation of pharmaceutical agents (abstract) that increase the half-life of the therapeutic (Feige et al, page 1, lines 19-20), wherein Fc is a vehicle that reduces immunogenicity and increases the biological activity by preventing degradation of the therapeutic (Feige et al., page 18, lines 21-24). The person of ordinary skill in the art would have expected success because the method of generating Fc fusion proteins was practised in the pharmaceutical industry for in vivo use at the time the invention was made.

19. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

20. Claims 12 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woolf et al. (International Application publication number WO 03/016475 A2, filed on 14 August 2002, in view of Lee et al (U.S. Patent No. 6,891,082, filed on 24 April 2001), and Feige et al (International Application publication No. WO 01/83525 A2, dated 8 November 2001), as evidenced by Godowski et al. (US Patent No. 6121415, dated 19 September 2000).

21. Claims 12 and 17 recite the concentrations of ActRIIB fusion peptide to be administered, and the increase in half life of the fusion peptide exceeding 5 days.

22. The teachings of Woolf et al, Lee et al and Feige et al are set forth above.

23. Woolf et al, Lee et al and Feige et al do not teach concentrations of ActRIIB fusion peptide and the increase in half life of the fusion peptide to more than 5 days.

24. However, since the disclosure does not specify criticality of the claimed ranges of dose, or the extent of the half life increase of the fusion ActRIIB peptide, optimization within prior art conditions or through routine experimentation is obvious to one skilled in the art.

As stated in MPEP 2144.05:

"The differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." "The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages". *In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382; Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 UDPQ2d 1843 (Fed. Cir.).*

25. It would have been, therefore, obvious to the person of ordinary skill in the art at the time the claimed invention was made to determine the optimal amounts of the ActRIIB fusion peptide required to be present in the composition. It would also have been obvious to the skilled artisan to design the fusion peptide by modifying the Fc region for modulating the pharmacokinetic properties, such as half-life of the therapeutic, since such properties are specified by the Fc region (Godowski et al., col 36, lines 26-30), Furthermore, the IgG molecules have an in vivo half life of 21 days. The person of ordinary skill in the art would have been motivated to perform such tests, to assess the effective dose of the fusion peptide and select the Fc domain required for increasing muscle mass. The person of ordinary skill in the art would have expected success because Fc

fusion peptides were used pharmaceutically at the time the invention was made.

26. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Double Patenting

Non-Statutory

27. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

28. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

29. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

30. Claims 1-5, 10-17, 23, 29-35, 40-44, are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 29-30, 32-33, 36, 43-49, 51-52, 54-60, 68, 77, of U.S. Patent Application

number 11/835,248, dated 17 April 2008. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to a method of treating a muscle or neuromuscular disorder, comprising increasing muscle mass, by administering a pharmaceutical composition comprising an ActRIIB fusion polypeptide comprising amino acids 23-138 of SEQ ID NO: 3, fused to an Fc portion of an antibody, wherein the fused peptide is capable of binding to GDF-8; wherein (i) the disease is a muscle disorder or a neuromuscular disorder such as muscular dystrophy or Duchenne muscular dystrophy; (ii) the Fc portion is modified to reduce effector function, binding to an Fc receptor and complement activation: (iii) the Fc fragment is a IgG1 or IgG4; and (iv) the amino acid sequence of the fusion peptide comprises at least 70 to 120 contiguous amino acids.

31. The only differences are as follows: (i) Claims 29, 36, 51 and 52, of the '248 application recite at least 80-90% identity with amino acids 23 to 138 of SEQ ID NO: 3 or to a fragment thereof, while the claims of the instant application recite at least 95% identity, thereby making the sequences of the '248 application a genus group comprising of at least 80% or more homologous sequences. (ii) Claims 29, 30, 32 and 33 of the '248 application recite treating or preventing of a muscle or neuromuscular disease, while the claims of the instant application are directed to increasing muscle mass in subjects having muscle or neuromuscular disorder. However, since both sets of claims recite the administration of ActRIIB-Fc fusion peptide in subjects having the same muscular disease, wherein the

peptide specifically binds to GDF-8, the resultant increase in muscle mass would inherently constitute treating such subjects. (iii) Claim 55 of the '248 application recites that the Fc portion comprises amino acids 148-378 of SEQ ID NO: 3, while claim 41 of the instant application does not characterize the sequence comprising amino acids 148 to 378 of SEQ ID NO: 3 as the Fc portion. However, this is inherent because the peptide of SEQ ID NO: 3 is 378 amino acids long, wherein amino acids 23 to 138 comprise the extracellular region of ActRIIB. Additionally, the instant specification teaches that amino acids 148 to 378 of SEQ ID NO: 3 constitutes the Fc portion of human IgG1 (page 18, lines 1-3). (iv) Claim 57 teaches that ActRIIB fusion polypeptide comprises an antibody constant region, while the claims of the instant application does not explicitly recite this phrase. However, claim 35 of the instant application recites the fusion polypeptide comprising of an unmodified Fc portion, that is equivalent to the constant region of the immunoglobulin or "Fc". Absent recitation of modifications of the constant region in the claim, a "constant region" would be interpreted as native or unmodified.

32. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

33. No claims are allowed.

34. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is (571)

272-9037. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 5:00 p.m.

35. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

36. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov/. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AD
3 June 2008

/Jeffrey Stucker/

Supervisory Patent Examiner, Art Unit 1649